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PATENT SPECIFICATION

NO DRAWINGS

1,178,400

Inventors: JANINE EBERLE, MICHELINE SERGANT, CLAUDE FAURAN and GERARD HUGUET

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International Classification:—C 07 c 87/02; C 07 d 87/28

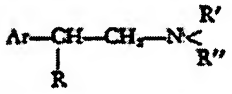
COMPLETE SPECIFICATION

Nitrogen Substituted Amines and their process of Preparation

We, DELALANDE S.A. of 32 Rue Henri-Regnault, Courbevoie, Hauts-de-Seine, France; a French body corporate do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns, as new industrial products having a therapeutic activity, compounds corresponding to the general formula:

(1)

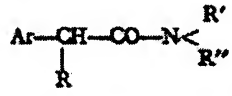


in which Ar represents a cycloheryl radical, a phenyl or naphthyl radical, which radical if desired, may be substituted by one or more amino or nitro groups, halogen atoms, hydroxy groups or alkoxy radicals having 1 or 2 carbon atoms, or a thienyl, furyl, quinolyl, benzimidazolyl, pyridyl, pyrazinyl, pyrimidinyl, quinoxalinyl or pyridazinyl radical.

R represents a saturated or unsaturated, linear or branched chain aliphatic radical having 1—5 carbon atoms, which radical if desired, may be substituted by an ethoxy, dimethyl-amino or hydroxy group,

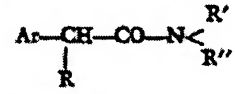
R′ and R″ each represent a hydrogen atom or an aliphatic radical having 1—3 carbon atoms, or R′ and R″ together with the nitrogen atom may form a heterocyclic radical such as a piperidino, morpholino or pyrrolidino radical.

According to the present invention, the process for the preparation of the compounds of the general formula (1) is characterised in that the corresponding amides of the general formula:



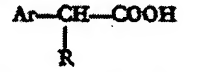
in which Ar, R, R′ and R″ are as defined in formula (1), are reduced by the action of a double hydride of lithium of by catalytic hydrogenation and the desired compounds are collected by usual means.

The process for the preparation of the corresponding amides of the general formula:



in which Ar, R, R′ and R″ are as defined in formula (1), is characterised in that an acid of the general formula:

(2)



in which Ar and R are as defined in formula (1), is reacted with a chlorinating agent such as thionyl chloride in order to obtain the corresponding acid chloride, which acid chloride is then reacted with an amine of the general formula:

(3)

in which R′ and R″ are as defined in formula (1), and the desired compound thereby obtained is collected by usual means, such as evaporation of the solvent and recrystallisation.

Preferably, the various phases of the process for the preparation of the corresponding amides are effected in a suitable organic solvent such as benzene, the chlorination reaction is carried out at the reflux temperature of the reaction medium, whilst the amination reaction is carried out at a temperature between —10° C and +10° C, more preferably 0° C.

The acid of the general formula (2) may be prepared either by alkylation of an acid of the general formula:

(4)

$$Ar—CH_2—COOH$$

with an alkyl halide of the general formula:

(5)

$$Hal—R$$

in which Ar and R are as defined in formula (1), and Hal represents a halogen atom, the reaction being carried out in liquid ammonia or benzene and in the presence of sodamide and at the boiling temperature of the reaction medium, or by alkylation of a nitrile of the general formula:

(6)

$$Ar—CH_2—C{\equiv}N$$

in which Ar is as defined in formula (1), by the process described for alkylation of the acid of the general formula (4) in order to obtain a substituted nitrile of the general formula:

(7)

$$Ar—\underset{\displaystyle R}{\underset{|}{CH}}—C{\equiv}N$$

in which Ar and R are as defined in formula (1), which is then hydrolysed according to conventional processes.

The corresponding amides may also be prepared by alkylating an amide of the general formula:

(8)

$$Ar—CH_2—CO—N<^{R'}_{R''}$$

in which Ar, R′ and R″ are as defined in formula (1), with an alkyl halide of the general formula (5) by the above-mentioned process or with a mixed organomagnesium compound of suitable formula.

According to a further embodiment of the present invention, the compounds of the general formula (1) may also be prepared from nitriles of formula (7) which are reduced with a double lithium and aluminium hydride, or by catalytic hydrogenation so as to obtain the corresponding primary amine which is then alkylated on the nitrogen atom with an alkyl halide of the general formula:

(9)

$$Hal—R' \text{ or } Hal—R''$$

in which R′ and R″ are as defined in formula (1), and Hal represents a halogen atom, or when R′ and R″ are CH_3 by the action of a formaldehyde-formic acid mixture.

In a particular method, given by way of example only, the amines of formula (1) in which Ar is a heterocyclic radical may be prepared either by the Mannich reaction on derivatives of the general formula:

(10)

$$Ar—CH_2—R$$

in which Ar is a heterocyclic radical and R is as defined in formula (1) by employing the amine corresponding to the desired derivative, or by the action of an alkyl halide of formula (5) on the carbon atom in the α-position with respect to the heterocyclic radical of an amine of the general formula:

(11)

$$Ar—CH_2—CH_2—N<^{R'}_{R''}$$

in which Ar is a heterocyclic radical, and R′ and R″ are as defined in formula (1).

Since the compounds of general formula (1) are bases, the present invention also concerns the salts they yield with mineral or organic acids.

According to the present invention, these salts are prepared by the action of selected acids on the corresponding base by conventional means.

The present invention will be further described with reference to the following non-limitative Example. Examples I to V relate to the preparation of the corresponding amides from which the amines of the present invention are prepared.

EXAMPLE I.

N, N-dimethyl - 3 - methyl - 2 - α - naphthyl pentanamide.

According to the schematic process

$$Ar—\underset{\displaystyle R}{\underset{|}{CH}}—COOH \rightarrow Ar—\underset{\displaystyle R}{\underset{|}{CH}}—CON<^{R'}_{R''}$$

a) 3 - methyl - 2 - α - naphthyl pentanoic acid was first prepared by the process

$$Ar\ CH_2\ COOH \rightarrow Ar—\underset{\displaystyle R}{\underset{|}{CH}}—COOH,$$

as follows:

A suspension of sodamide (1 mol) is prepared in liquid ammonia, and 0.5 mol of α-naphthyl acetic acid is added thereto. After half an hour (i.e. after an orange colouration is obtained), 0.5 mol of secondary butyl bromide is added. The mixture is left under reflux for 2 hours. After evaporation of the ammonia and hydrolysis, extraction is effected with ether.

The acid obtained is separated by distillation.

B.pt/0.1 mm Hg = 175° C. yield = 83%.

b) then the desired compound N, N-dimethyl-3 - methyl - 2 - α - naphthyl pentanamide is prepared as follows:

2.22 mols of thionyl chloride are added to a benzene solution (100 ml) of 0.73 mol of the acid thus prepared. After one hour under reflux, any excess thionyl chloride is removed.

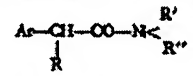
Then a benzene solution (600 ml) of the acid chloride thus prepared is added to a solution, cooled to 0° C, of dimethylamine (3 mols) in anhydrous ether. After treatment in water, the organic phase is washed with dilute soda. By evaporation of the benzene, a residue is obtained which is the desired product and is crystallised from isopropyl ether:

M.pt. = 110° — 122° C (yield = 82%).

Analysis = $C_{15}H_{21}NO$

N% calculated 5.20, found 5.22

Certain compounds of the general formula:



in which Ar, R, R' and R'' are as defined in formula (I), and which were prepared by the above-mentioned process are shown in Table I.

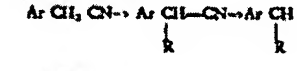
TABLE I

Ar	R	NR'R''	Empirical Formula	Molecular Weight	N% Theory	N% Found	B.pt °C/ p mm Hg	m.pt. °C	n_D^{20}
C_6H_5	n—C_6H_{11}	$N(CH_3)_2$	$C_{13}H_{27}NO$	233.34	6.00	6.12	134—6/1.5		1.5122
C_6H_5	n—C_8H_4	$N(CH_3)_2$	$C_{15}H_{21}NO$	191.26	7.32	763	121/3		1.5265
C_6H_4S	sec—C_4H_9	$N(CH_3)_2$	$C_{14}H_{23}NOS$	225.35	6.21	5.96	120—125/0.6	50°C	

EXAMPLE II

N,N - dimethyl - 2 - (4 - chlorophenyl - 4-methyl pentanamide.

a) First, 2 - (4 - chlorophenyl) - 4 - methyl pentanoic acid is prepared according to the schematic process.



as follows:

An ether solution of 4 - chlorophenyl acetonitrile (0.2 mol) is added to a suspension of 0.2 mol sodamide in liquid ammonia. After 40 minutes 0.2 mol of secondary butyl bromide is added and the reaction is continued for 1 hour. Hydrolysis is then effected in the usual manner.

The distilled α-alkylated nitrile B.pt./0.5 mm Hg = 199° C) is obtained in a yield of 65%.

The alkylated nitrile (0.1 mol) is then hydrolysed for 12 hours under reflux by means of a mixture of equal parts of acetic acid, sulphuric acid and water. The reaction mixture is then diluted with water and extracted with ether. The volatile phase is removed by 5% soda solution. After acidification, an oily residue of the desired product is obtained which is recrystallized in heptane: m.pt. = 115° C, yield = 55%.

b) According to the same schematic process as in Example 1, the resultant acid (0.51 mol) is treated with thionyl chloride (0.8 mol) under reflux. After 1 hour the excess thionyl chloride is removed, and the residue in a benzene solution is treated directly with dimethylamine. After addition of water, the organic phase is decanted, dryed and concentrated. In this way the desired product is obtained having a m.pt = 70° C and in a yield of 73%.

Analysis = $C_{14}H_{20}$ Cl N O

N% calculated 5.32, found 5.46.

Compounds shown in Table II are prepared according to the process described in example II.

TABLE II

Ar	R	N'R''	Empirical Formula	Molecular Weight	N% Theory	N% Found	B.pt. °C/ p mm Hg	m.pt °C	n $^{20}_{D}$
p—$NO_2C_6H_4$	sec—C_4H_9	$N(CH_3)_2$	$C_{14}H_{20}N_2O_3$	264.32	10.60	10.70			
p—$NH_2C_6H_4$	sec—C_4H_9	$N(CH_3)_2$	$C_{14}H_{22}N_2O$	234.33	11.96	11.87		110°C	
p—$NH_2C_6H_4$	sec—C_4H_9	$N(CH_3)_2$ HCL salt	$C_{14}H_{23}ClN_2O$	270.79	10.35	10.15		210°C	

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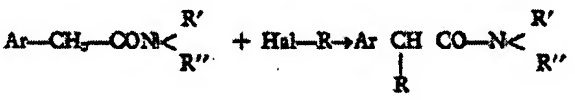
EXAMPLE III.

N, N - dimethyl - 2 - phenyl - 4 pentynamide.

This compound is obtained according to the schematic process



as follows:

An ether solution of N, N - dimethyl-phenylacetamide (0.16 mol) is added to a suspension of sodamide (0.16 mol) in liquid ammonia. After one quarter of an hour a volatile solution of propargyl bromide (0.16 mol) is added and the reaction continued for a further 1 hour. After evaporation of the ammonia and hydrolysis, extraction is effected with ether. By distillation (E/0.2= 135° C) 18.5g of the desired product is obtained.

Analysis $C_{13}H_{15}N$ O
N% calculated 6.96, found 6.96.

According to the same process, N, N-dimethyl-2 - phenyl - 4 pentanamide was prepared: Ed/0.05 = 137−138° C.

Analysis: $C_{13}H_{17}N$ O
N% calculated 6.88, found 6.96.

EXAMPLE IV.

N, N - dimethyl - 5 - dimethylamino - 2-phenyl pentanamide.

According to the same schematic process as in Example III, N, N - dimethyl - 5 - dimethylamino - 2 - phenyl pentanamide was prepared as follows: 0.5 mol of sodamide was added to a benzene solution of 0.5 mol N, N-dimethyl phenyl acetamide. After 2 hours under reflux, the mixture is cooled to 40° C and a benzene solution of 0.5 mol of dimethylamino-chloropropane is added. The solution is kept under reflux for a further four hours. Hydrolysis is effected and by treatment of the organic phase a residue of the desired product is obtained which is distilled (B.pt/0.25 mm Hg. = 150° C) (yield = 40%).

Analysis: $C_{14}H_{24}N$ O
N% calculated 11.28, found 11.15.

Certain compounds which were prepared according to the process described in Example IV are shown in Table III.

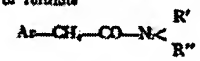
Table III

Ar	R	NR'R''	Empirical Formula	Molecular Weight	N% Theory	N% Found	B.pt. °C/ p mm Hg	m.pt °C	n^{20}
C_6H_5	C_5H_{11} iso	$N(CH_3)_2$	$C_{13}H_{23}N\ O$	233.34	6.00	6.05	131—3/1.5		1.5128
C_6H_5	C_3H_7 iso	$N(CH_3)_2$	$C_{12}H_{17}N\ O$	205.29	6.82	6.94	121—4/3	60	
C_6H_5	C_4H_9 sec.		$C_{15}H_{23}N\ O$	261.35	5.35	5.43	137—9/0.1		1.5339
C_6H_5	nC_3H_7	$N(CH_3)_2$	$C_{12}H_{17}N\ O$	205.29	6.82	6.89	124/2	54	
C_6H_5	C_6H_9 iso	$N(CH_3)_2$	$C_{14}H_{21}N\ O$	219.32	6.39	6.24		114	
C_6H_5	$CH_2CH_2OC_2H_5$	$N(CH_3)_2$	$C_{14}H_{21}N\ O_2$	235.32	5.95	6.18	134/0.3		1.5138

EXAMPLE V.

N,N - dimethyl - 3 -hydroxy - 3 - methyl-2 - phenyl - pentanamide.

This compound was prepared by the action of a mixed organomagnesium compound on a compound of formula



as follows:

An ether solution of 0.5 mol of isopropyl magnesium bromide is added to a benzene solution of 0.5 mol of N, N dimethyl-phenyl-acetamide. After heating for 1 hour under reflux 0.5 mol of 2 - butanone is introduced. The solution is kept under reflux for 2½ hours. After hydrolysis in a hydrochloric acid medium and extraction with ether, an oily residue is obtained which is crystallized from hexane to give the above compound: m.pt = 68° C (yield = 60%).

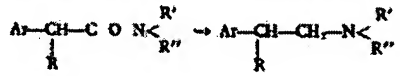
Analysis $C_{13}H_{19}N\ O_2$

N% calculated 5.95, found 6.19.

EXAMPLE VI.

1 - Dimethylamino - 3 - methyl 2 - (alpha-naphthyl) - pentane.

This compound is prepared by the schematic process



as follows:

0.1 mol of N, N-dimethyl - 3 - methyl-2-(alpha-naphthyl) pentanamide prepared according to example 1, is added to a suspension of 0.1 mol of $LiAlH_4$ in 300 ml anhydrous ether.

After 4 hours under reflux, hydrolysis is effected. After filtration, the volatile solution is extracted with 4N—HCl and the above organic compound which is salted out is distilled.

B.pt/0.3 mm Hg. = 133—135° C (yield = 75%).

Analysis $C_{16}H_{23}N$

		C	H	N
Calculated	%	84.65	9.87	5.48
Found	%	84.45	9.81	5.37

Its hydrochloride melts at 224° C.

Analysis $C_{16}H_{24}N\,Cl$

		C	H	N	Cl
Calculated	%	74.07	8.98	4.80	12.15
Found	%	74.27	9.06	4.84	12.13

EXAMPLE VII.

1 - Dimethylamino - 3 - methyl - 2[(5-chloro - 2 - methoxy) phenyl] pentane.

According to the same process as that of Example VI, 1 - dimethylamino - 3 - methyl-2 - [(5 - chloro - 2 - methoxy) phenyl] pentane was prepared as follows:

A solution of N,N-dimethyl (2-methoxy-5-chloro) phenyl acetamide (0.78 mol) is added to a suspension of sodamide in liquid ammonia and is then treated with 0.78 mol of secondary butyl bromide. After 2 hours, hydrolysis and extraction with ether is effected. By concentration of the volatile solution, a crude product is obtained which, after chromatographic analysis, is directly treated with $Al\,Li\,H_4$ (0.69 mol) in anhydrous ether. After 4 hours under reflux and addition of water and soda, the desired amine is obtained which is distilled:

B.pt/1.5 mm Hg. = 115° C (75%).

Analysis $C_{15}H_{24}ClN\,O$

		C	H	N
Calculated	%	66.77	8.97	5.19
Found	%	66.74	8.98	5.39

After dissolving in ethanol and treatment with gaseous hydrochloric acid, the hydrochloride is obtained which is dried and is then recrystallised in acetone.

m.pt. = 178° C.

Analysis $C_{15}H_{25}Cl_2N\,O$

		C	H	N
Calculated	%	58.82	8.23	4.57
Found	%	58.67	8.05	4.39

Certain compounds of the general formula (I) and which were prepared by the process described in Examples VI and VII are shown in Table IV.

TABLE

Ar	R	NR'R"	Salt	Empirical Formula	Molecular weight
C_6H_5	$CH_2—CH=CH_2$	$N(CH_3)_2$		$C_{12}H_{15}N$	189.29
C_6H_5	$CH_2—CH=CH_2$	$N(CH_3)_2$	HCl	$C_{13}H_{20}NCl$	225.76
C_6H_5	C_5H_{11}n	$N(CH_3)_2$		$C_{13}H_{23}N$	219.36
C_6H_5	C_5H_{11}n	$N(CH_3)_2$	HCl	$C_{13}H_{24}NCl$	255.82
C_6H_5	C_4H_9n	$N(CH_3)_2$		$C_{12}H_{19}N$	177.28
C_6H_5	C_4H_9n	$N(CH_3)_2$	HCl	$C_{12}H_{20}NCl$	213.75
C_6H_5	C_5H_{11} iso	$N(CH_3)_2$		$C_{13}H_{23}N$	219.36
C_6H_5	C_5H_{11} iso	$N(CH_3)_2$	HCl	$C_{13}H_{24}NCl$	255.82
C_6H_5	C_5H_9 iso	$N(CH_3)_2$		$C_{13}H_{21}N$	191.30
C_6H_5	C_5H_9 iso	$N(CH_3)_2$	HCl	$C_{13}H_{22}NCl$	227.77
C_6H_5	$CH_2—C\equiv CH$	$N(CH_3)_2$		$C_{13}H_{17}N$	187.27
C_6H_5	$CH_2—C\equiv CH$	$N(CH_3)_2$	HCl	$C_{13}H_{18}NCl$	223.74
C_6H_5	C_5H_7n	$N(CH_3)_2$		$C_{13}H_{21}N$	191.30
C_6H_5	C_5H_7n	$N(CH_3)_2$	HCl	$C_{13}H_{22}NCl$	227.77
C_6H_5	$(CH_2)_2N(CH_3)_2$	$N(CH_3)_2$		$C_{15}H_{26}N_2$	234.37
C_6H_5	$(CH_2)_2N(CH_3)_2$	$N(CH_3)_2$	2HCl	$C_{15}H_{28}N_2Cl_2$	307.30
C_6H_5	C_4H_9 sec			$C_{16}H_{25}NO$	247.37
C_6H_5	C_4H_9 sec		HCl	$C_{16}H_{26}NOCl$	283.83
C_6H_5	C_4H_9 iso	$N(CH_3)_2$		$C_{14}H_{23}N$	205.33
C_6H_5	C_4H_9 iso	$N(CH_3)_2$	HCl	$C_{14}H_{24}NCl$	241.80
C_6H_5	$CH_2—\underset{\displaystyle C_2H_5}{\overset{\displaystyle OH}{\underset{\displaystyle |}{\overset{\displaystyle |}{C}}}}$	$N(CH_3)_2$		$C_{14}H_{23}NO$	221.33
C_6H_5	$CH_2—\underset{\displaystyle C_2H_5}{\overset{\displaystyle OH}{\underset{\displaystyle |}{\overset{\displaystyle |}{C}}}}$	$N(CH_3)_2$	HCl	$C_{14}H_{24}NOCl$	257.80

IV

Elementary analysis								B.pt/ p.mm.Hg.	m.pt°C	n^{20}
Theory				Found						
C	H	N	Cl	C	H	N	Cl			
82.48	10.12	7.40		82.37	10.08	7.52		104°C/9		1.5055
69.16	8.93	6.20	15.71	68.99	9.07	6.07	15.67		122—3°C	
82.13	11.49	6.39		82.08	11.36	6.62		111—2°C/3		1.4912
70.42	10.24	5.48	13.86	70.39	10.19	5.62	13.73		164—5°C	
81.30	10.80	7.90		81.17	10.74	8.10		94—5°C/10		1.4969
67.43	9.43	6.55	16.59	67.29	9.36	6.32	16.70		173°C	
82.13	11.49	6.39		81.97	11.43	6.34		128°C/10		1.4902
70.42	10.24	5.48	13.86	70.30	10.11	5.45	14.47		184°C (dec.)	
81.60	11.06	7.32		81.55	11.06	7.20		100—2°C/10		1.4973
68.55	9.74	6.15	15.56	68.65	9.93	6.15	16.36		218—20°C	
83.37	9.15	7.48		83.37	9.25	7.39		86—7°C/2		1.5182
69.78	8.11	6.26	15.85	69.75	8.30	6.30	15.70		162°C	
81.61	11.07	7.32		81.93	10.99			104—6°C/10		1.4937
68.55	9.74	6.15	15.56	68.48	9.94	6.19	15.38		139°C	
77.68	10.19	5.66		77.88	9.99	5.73		128—9/2		1.5156
67.70	9.23	4.93	12.49	67.53	9.20	5.03	12.38		178—80 (dec.)	
81.88	11.29									
69.54	10.01	5.79	14.66							
75.97	10.47	6.33		75.63	10.18	6.33		101°C/0.1		1.5123
65.22	9.38	5.43	13.75	65.12	9.20	5.36	13.69		160°C	

TABLE IV

Ar	R	NR'R"	Salt	Empirical Formula	Molecular weight
p.ClC_6H_4	C_3H_9 sec	$N(CH_3)_2$		$C_{14}H_{22}NCl$	239.78
p.ClC_6H_4	C_3H_9 sec	$N(CH_3)_2$	HCl	$C_{14}H_{23}NCl_2$	276.25
C_6H_5	$CH_2CH_2OC_2H_5$	$N(CH_3)_2$		$C_{15}H_{25}NO$	221.33
C_6H_5	$CH_2CH_2OC_2H_5$	$N(CH_3)_2$	HCl	$C_{15}H_{26}ClNO$	257.80
C_4H_3S	C_3H_9 sec	$N(CH_3)_2$		$C_{12}H_{21}NS$	211.36
C_4H_3S	C_3H_9 sec	$N(CH_3)_2$	HCl	$C_{12}H_{22}ClNS$	247.83
p.$NH_2C_6H_4$	C_3H_9 sec	$N(CH_3)_2$		$C_{14}H_{24}N_2$	220.35
p.$NH_2C_6H_4$	C_3H_9 sec	$N(CH_3)_2$	2HCl	$C_{14}H_{26}Cl_2N_2$	293.28
p(OCH_3)C_6H_4	C_3H_9 sec	$N(CH_3)_2$		$C_{15}H_{23}NO$	235.36
p(OCH_3)C_6H_4	C_3H_9 sec	$N(CH_3)_2$	HCl	$C_{15}H_{24}ClNO$	271.83
p.OHC_6H_4	C_3H_9 sec	$N(CH_3)_2$	HCl	$C_{14}H_{24}ClNO$	257.80

EXAMPLE VIII.

1 - Amino - 3 - methyl - 2 phenyl pentane. This compound was prepared according to the schematic process

$Ar—\underset{\underset{R}{|}}{CH}—C{\equiv}N \rightarrow Ar—\underset{\underset{R}{|}}{CH}—CH_2—NH_2$, as follows:

TABLE

Ar	R	NR'R"	Salt	Empirical Formula	Molecular Weight
α—$C_{10}H_7$	sec C_3H_9	NH_2		$C_{16}H_{21}N$	227.34
α—$C_{10}H_7$	sec C_3H_9	NH_2	HCl	$C_{16}H_{22}NCl$	291.85
C_6H_{11}	sec C_3H_9	NH_2		$C_{13}H_{25}N$	183.32

EXAMPLE IX.

1 - Dimethylamino - 3 - methyl - 2 - phenyl-pentane.

This compound was prepared according tothe schematic process:

$Ar—\underset{\underset{R}{|}}{CH}—CH_2—NH_2$ (prepared according to Example 8)$\rightarrow$ $Ar—\underset{\underset{R}{|}}{CH}—CH_2—N\langle^{R'}_{R''}$

as follows:

(Continued)

Elementary analysis								B.pt/ p.mm Hg	m.pt°C	n^{20}
Theory				Found						
C	H	N	Cl	C	H	N	Cl			
70.12	9.25	5.84		70.01	9.28	5.75		95—8°C/0.1		1.5131
60.87	8.39	5.07		60.80	8.54				210—5°C (dec.)	
75.97	10.47	6.33		75.85	10.25	6.38		107°C/3		1.4911
65.22	9.38	5.43	13.75	65.34	9.52	5.58	13.89		155°C	
68.19	10.02	6.63		68.10	9.75	6.54				
58.15	8.95	5.65	14.30	58.33	8.84	5.58	14.21		200°C (dec.)	
76.31	10.98	12.71		76.39	10.81	12.88		115—120/0.1	240—5° (dec.)	
57.33	8.94	9.55	24.17	57.41	9.05	9.33	23.97			
								136—7/5		
66.27	9.64	5.15	13.04	66.49	9.67	5.18	12.95		187°C	
65.22	9.38	5.43		65.33	9.45	5.40			160—5°C	

0.2 mol of 1 - cyano - 2 - methyl - 1 - phenyl butane dissolved in 40 ml anhydrous ether is added to a suspension of 0.2 mol of $LiAlH_4$ in 400 ml anhydrous ether. After 4 hours under reflux hydrolysis is effected, the volatile solution is concentrated, and a residue is obtained which is distilled to obtain the desired product.

B.pt./20 mm Hg. = 134° C.

Certain compounds of the general formula (1) and which were prepared by the process described in Example VIII are shown in Table V.

V

Elementary Analysis								B.pt./ pmm Hg °C	m.pt	n^{20}.
Theory				Found						
C	H	N	Cl	C	H	N	Cl			
84.53	9.31	6.16		84.46	9.47	6.14		140/0.2		1.5888
72.84	8.41	5.31	13.44	72.88	8.41	5.39	13.26			
								134/20		

A mixture of 0.1 mol of 1 - amino - 3-methyl - 2 - phenyl pentane is placed under reflux for 12 hours with 0.5 mol of formic acid (98%) and 0.22 mol of 30% formaldehyde solution. Then 10 ml of concentrated HCl is added before evaporating to dryness. The residue is taken up with water, the solution rendered alkaline and extracted with ether. The above di-substituted amine is obtained by distillation.

B.pt./4 mm Hg. = 97—98° C (yield = 60%).

Certain compounds of the general formula (1) and which are prepared by the process described in Example IX are shown in Table VI.

TABLE

Ar	R	NR'R"	Salt	Empirical Formula	Molecular Weight
C_6H_{11}	sec C_4H_9	$N(CH_3)_2$		$C_{14}H_{29}N$	211.38
C_6H_{11}	sec C_4H_9	$N(CH_3)_2$	HCl	$C_{14}H_{30}ClN$	

EXAMPLE X.

1 - Dimethylamino - 3 - methyl - 2(2-quinolyl) pentane.

This compound was prepared according to the method of applying the Mannich reaction to the $Ar—CH_2—R$, derivatives in the following manner:

a) 2 - methyl - 4 - (2 - quinolyl) butane, was first prepared by adding 0.5 mol quinaldine to a suspension of 0.5 mol sodamide in liquid ammonia, and after 2 hours 0.5 mol of secondary butyl bromide is introduced. After evaporation of the ammonia, extraction is effected with ether and distillation carried out to give the desired product.

B.pt./9 mm Hg. = 149° C (yield = 60%).

b) 1 - Dimethylamino - 3 - methyl - 2(2-quinolyl) pentane was prepared from this compound by the following process:

A mixture of 0.165 mol of the butane derivative, 0.5 mol of dimethylamine hydrochloride, 15g trioxymethylene and 100 ml amyl alcohol is kept under reflux with stirring for 10 minutes, 100 ml of water is then added, the aqueous solution is rendered alkaline with concentrated soda, extracted with ether and concentrated. The residue is distilled to give the desired product:

B.pt./8 mm Hg. = 175—176° C (yield = 70%).

Analysis: $C_{17}H_{24}N_2$

		C	H	N
Calculated	%	79.64	9.44	10.93
Found	%	79.54	9.27	11.27

According to the same process 1 dimethylamino - 3 - methyl - 2 - (2 - quinoxalyl) pentane was prepared

B.pt./0.05 mm Hg. = 137—138° C

Analysis = $C_{16}H_{23}N_3$

		C	H	N
Calculated	%	74.66	9.01	16.33
Found	%	74.44	9.07	16.37

EXAMPLE XI.

1 - Dimethylamino - 2 - (2 - pyridyl) - 3-methyl pentane.

This compound was prepared according to the schematic process

$$Ar—CH_2—CH_2—N<\begin{matrix}R'\\R''\end{matrix} + Hal—R_3$$

as follows:

An ether solution of dimethylamino - 2-ethyl pyridine (0.5 mol) was added to a suspension of sodamide in liquid ammonia (0.5 mol). After 2 hours under reflux 0.5 mol of secondary butyl bromide is added and the solution is reacted for 2 hours.

After evaporation of the ammonia, the solution is taken up in 400 ml water and 400 ml ether. The volatile phase, decanted and then concentrated, gives the above compound in the form of an oily residue which is distilled

B.pt./0.3 mm Hg. = 85° C yield = 81%.

Analysis: $C_{13}H_{22}N_2$

		C	H	N
Calculated	%	75.67	10.75	13.58
Found	%	75.87	10.91	13.80

The resultant base is treated in solution in ethyl acetate with the equivalent of maleic acid. The acid maleate is obtained by recrystallisation from a mixture of isopropyl alcohol and isopropyl ether (1/4). m.pt = 100—102° C.

Analysis: $C_{17}H_{26}N_2O_4$

		C	H	N
Calculated	%	63.34	8.13	8.69
Found	%	63.22	7.88	8.74

1 - Dimethylamino- (2 - pyridazinyl) 3-methyl pentane was also prepared in the same manner

Analysis: $C_{12}H_{21}N_3$

		C	H	N
Calculated	%	69.52	10.21	20.27
Found	%	69.30	10.00	20.45

and its monomaleate:

Analysis: $C_{16}H_{25}N_3O_4$

		C	H	N
Calculated	%	59.42	7.79	13.00
Found	%	59.39	7.75	12.88

The above-mentioned compounds accord-

VI

Elementary Analysis								B.pt./ pmm Hg°C	m.pt.	n^{20}
Theory				Found						
C	H	N	Cl	C	H	N	Cl			
79.54	13.83	6.63		79.66	13.85	6.74		97—8°/4		
67.84	12.20	5.65	14.31	67.81	11.98	5.57	14.39			

ing to the present invention were studied on animals in the laboratory and it was possible to demonstrate cardio-vascular, diuretic and spasmolytic activities of an interesting nature.

A) Cardio-vascular activity

When administered by intra-venous injection to dogs, cats, rabbits or rats, some of the described substances, in particular the hydrochloride of 1 - dimethylamino - 3 - methyl-2 - (α - naphthyl) pentane and the hydrochloride of 1 - dimethylamino - 3 - methyl-2 - cyclohexyl - pentane cause hypotension.

However, other substances such as the hydrochloride of 1 - dimethylamino - 3-methyl - 2[(5 - chloro 2 - methoxy)phenyl] pentane and the monomaleate of 1 - dimethylamino 2 - (2 - pyridyl) - 3 - methyl - pentane cause lasting hypotension.

Substances having a hypertensive effect cause peripheral vaso constriction shown by the amount of the supply of an intra-arterial transfusion effected under constant pressure on rabbits, the products being administered directly in the transfusion.

B) Diuretic activity

Some of the described substances have interesting diuretic properties observed on rats and dogs and have a bearing on the elimination of water and ions. This concerns more particularly 1 - dimethylamino - 3 -methyl-2 - (5 - chloro - 2 methoxy) - phenyl pentane hydrochloride and 1 - dimethylamino-(2 - pyridyl) - 2 - methyl pentane monomaleate.

C) Spasmolytic action

Some derivatives have a spasmolytic action demonstrated on the isolated duodenum of the rat and on the uterus in situ, in particular 1 - dimethylamino - 2 - phenyl heptane hydrochloride.

Some of these derivatives have been studied particularly, for example:

1) 1 - dimethylamino - 3 - methyl - 2-(5 - chloro - 2 methoxy) - phenyl pentane hydrochloride; its diuretic activity is shown on rats in a dose of 5mg/kg administered orally and on dogs in a dose of 25mg/kg administered intraduodenally. The product is hypotensive from 2mg/kg administered intravenously on dogs and rabbits. It is slightly vasodilatatory. Moreover, it has a vagolytic activity: it suppresses the tensional effects of acetyl choline and vagal excitation and on the isolated organ it has atropinic properties.

Its LD 50 is 115mg/kg orally and 25mg/kg intravenously on mice.

2) 1 - dimethylamino - 3 - methyl - 2-(1 - naphthyl) pentane hydrochloride.

This produce is hypertensive from 0.5mg/kg on dogs intravenously. It has a vasoconstrictor effect in a dose of 250 /kg injected in the artery whose supply is being studied. It has mixed spasmolytic, papaverinic and atropinic properties, the first being equivalent to 0.5 part of papaverine on the isolated duodenum of the rat treated with barium chloride and on the uterus of the rat in situ: the second equivalent to 0.01 part of atropine.

Its LD 50 is 15.5mg/kg intravenously and 100mg/kg orally on mice.

These cardio-vascular, diuretic and spasmolytic properties make the derivatives of the present invention useful medicines in the treatment of various ailments such as hypertension, circulatory disorders of the extremities, oedamas and spasmodic ailments.

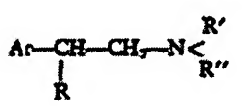
The present invention also concerns the various pharmaceutical compositions for administration orally, for rectal parenteral or local administration and comprise one or more of the derivatives of formula I and/or their salts and an excipient.

These pharmaceutical compositions may be simple tablets, sugar-coated pills or pellets for intestinal or delayed disintegration capsules, solutions to be taken orally or injected, suppositories, creams, pommades or lotions and are prepared according to the art with suitable excipients for the selected form, such as talcum, starch, lactose, magnesium stearate, polyoxyethylene-glycols, resins, gelatine, aqueous or oily vehicles, natural or synthetic excipients for suppositories, creams and pommades, colouring agents, aromatic agents, wetting agents, and various buffers.

The active therapeutic doses depend on the subject and gravity of the case. In general, the unit dose taken orally by humans is from 0.001 to 0.1g.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:



(1)

in which Ar represents a cyclohexyl radical, a phenyl or naphthyl radical or a thienyl, furyl, quinolyl, benzimidazolyl, pyridyl, pyrazinyl, pyrimidinyl, quinoxalinyl or pyridazinyl radical,

R represents a saturated or unsaturated, linear or branched-chain aliphatic radical having 1 to 5 carbon atoms,

R′ and R″ each represent a hydrogen atom, an aliphatic radical having 1 to 3 carbon atoms or R′ and R″ together with the nitrogen atom form a heterocyclic radical.

2. The acid addition salts of the compounds according to claim 1.

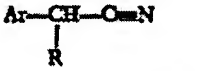
3. A compound according to claim 1 in which Ar represents a phenyl or naphthyl radical substituted by one or more amino or nitro groups, halogen atoms, hydroxy groups or alkoxy radicals having 1 or 2 carbon atoms.

4. A compound according to claim 1 in which R represents an aliphatic radical substituted by an ethoxy, dimethylamino or hydroxy group.

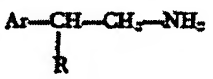
5. A compound according to claim 1 in which R′ and R″ together with the nitrogen atom form a piperidino, morpholino or pyrrolidino radical.

6. A process for the preparation of the compounds according to claim 1, characterised in that the corresponding amides of the general formula Ar—CH(R)—CO—NR′R″, in which Ar, R, R′ and R″ are as defined in formula (1) are reduced by the action of a double hydride of lithium and aluminium or by catalytic hydrogenation and the desired compounds are collected by the usual means.

7. A process for the preparation of the compounds according to claim 1, comprising reducing a nitrile of the formula:



in which Ar and R have the significance mentioned in claim 1, with a double lithium and aluminium hydride, or by catalytic hydrogenation so as to obtain the corresponding primary amine of the formula:



which is then alkylated with an alkyl halide of formula:

Hal—R′ or Hal—R″

in which R′ and R″ have the significance mentioned in claim 1, and Hal represents a halogen atom, or when R′ and R″ are CH_3 by the action of a formaldehyde-formic acid mixture, and the desired derivatives are collected by usual means.

8. A process for the preparation of the compounds according to claim 1, in which Ar is a heterocyclic radical characterised in that a derivative of formula:

Ar—CH_3—R

in which Ar is a heterocyclic radical and R is as defined in formula (1) is treated by the Mannich reaction employing the amine corresponding to the desired derivative.

9. A process for the preparation of the acid addition salts of the derivatives according to claim 2, characterised in that a mineral or organic acid is reacted with the selected derivative.

10. Pharmaceutical compositions intended for administration by oral, rectal, parenteral or local means and containing one or more of the derivatives according to claim 1 and/or their salts according to claim 2, together with suitable excipients.

11. Pharmaceutical compositions intended for administration by oral, rectal, parenteral or local means and containing one or more of the derivatives according to claim 1 and/or their salts according to claim 2 together with suitable excipients, in unit doses containing from 0.001 to 0.100 g. of active compound.

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